SCIENTIFIC ABSTRACT

The purpose of this study is to determine whether CD34+ cells from the bone marrow of HIV-1 infected children can be transduced by retroviral-mediated transfer of the anti-HIV-1 RevM10 cDNA, safely infused intravenously, resulting in subsequent engraftment and production of mature peripheral blood leukocytes containing and expressing RevM10. An initial clinical trial has demonstrated that RevM10-transduced peripheral lymphocytes have survival advantage over those without the active anti-HIV-1 gene. The currently proposed phase I study will test the hypothesis that transducing CD34+ stem cells with RevM10 leads to the development of lymphocytes with survival advantage, potentially resulting in their accumulation to levels, ideally, that are clinically relevant.

The study is open to children from three to thirteen years of age with HIV-1 infection who are on a stable drug regimen and without opportunistic infection. Bone marrow will be collected from each subject and CD34+ cells isolated. The CD34+ cells will be divided into two equal portions and transduced by either of two retroviral vectors, RVNL3-hM10 (containing the active RevM10 gene) or RVNL3-FX (untranslatable). Transduction will be augmented by recombinant thrombopoietin , stem cell factor and flt-3 ligand, using recombinant fibronectin CH-296 as a support matrix. After transduction, the cells will be re-mixed and infused intravenously back into the subject without prior cytoreductive therapy. Children will be maintained on their pre-treatment, or appropriately modified drug regimen, both during and after gene transfer.

Serial samples of peripheral blood will be analyzed for the frequency of cells containing the inserted active RevM10 or marker vectors. An increase in the frequency of lymphocytes containing the active RevM10 relative to those with the untranslated construct would demonstrate survival advantage of cells with this anti-HIV-1 gene. Determination of RevM10 RNA by RT-PCR in the gene-marked cell population would confirm active transcription of the anti-HIV-1 gene. If persistent production of cells containing and expressing the RevM10 gene is achieved, cells may even accumulate to levels that would potentially decrease viral load, roughly estimated to be 10% of peripheral lymphocytes.

In all, these studies will seek to determine the safety and feasibility of RevM10 gene transfer into bone marrow CD34+ cells to provide survival advantage to lymphocytes developing from the gene-modified progenitors. Ideally, sufficient engraftment of transduced CD34+ cells and optimal gene expression in progeny lymphocytes would lead to accumulation of protected lymphocytes, perhaps to clinically relevant levels.